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Response: A Quest and a Wager

Rick Bevins, Ph.D., Paul Kenny, Ph.D., and Jed Rose, Ph.D.

Paul Kenny: Dr. Markou's paper is a good overview of where we are in the quest for new pharmacological treatments for smoking addiction. The field is focusing mainly on the nicotinic receptors and the glutamate and GABA neurotransmitter systems. The nicotinic receptors regulate the effects of nicotine, and through these receptors, nicotine brings both glutamate and GABA into play.

Jed Rose: I think we are far from exploiting the full potential of nicotine itself as a replacement for smoking. At present, fewer than 10 percent of people using nicotine replacement therapy (NRT) achieve long-term smoking cessation. I think the success rate is low because we haven't yet learned to administer nicotine in a way that reproduces the full effect of nicotine obtained from smoking. Along with acute reinforcement, stress reduction, and cognitive enhancement, we also need to address the habit component—the constellation of sensory cues that develop around inhaling smoke.

Kenny: Do you believe that it's a viable strategy to consider medications that bypass the nicotinic receptor and instead work on other systems, like GABA and glutamate, that underlie the habitual aspects of smoking behavior?

Rose: Trying to modulate those downstream systems is an important strategy. However, I think it will likely be best used in combination with improved nicotine replacement. The difficulty of having a large impact on smoking without doing anything at the nicotine receptor should not be underestimated.

Rick Bevins: Combining pharmacological treatments with behavioral approaches is a must. There may be a place for combining medications, for example, targeting reinforcing effects with one and craving with another, or using one medication to alleviate the side effects of another. Such strategies are hinted at in the article but not addressed directly in a way that might encourage this approach.

Kenny: It seems very logical to give people the safest therapeutic that we know works, which right now would be NRT. And then, it seems like a good idea to have as many tools as possible to try to help those people for whom NRT is less effective. So that's where many of the compounds that the authors discuss come in, such as metabotropic glutamate receptor agonists or $GABA_B$ receptor agonists.

Bevins: The nicotine vaccine is another tool. One wouldn't use it with NRT, of course, because it prevents nicotine from getting to the brain, but it makes a nice adjunct to non-nicotine treatments. It doesn't have any central nervous system effects, so what you're hoping it will do, at least in my mind, is just to catch people who slip and get them back on the abstinence track.

Rose: I wouldn't totally rule out the idea that there might be creative combinations of NRT and nicotine vaccine, perhaps in a sequence where we use the former to wean

someone away from the smoking habit and then the latter to prevent its reestablishment. In general, however, the nicotine vaccine and other treatments that prevent nicotine from activating nicotinic receptors can help people partway, but not all the way, to long-term quitting. The reason is that these treatments don't replace the nicotine effects that motivate most people to smoke—stress relief, enhanced pleasure, weight control, cognitive enhancement, and so forth.

Bevins: A conundrum in treatment is that you want to reduce nicotine's impact on glutamate and dopamine neurotransmission enough to block the drug's motivating effects, but sustain enough neurotransmission to ward off symptoms of withdrawal. This is why it's important to learn exactly what each compound does at the various nicotinic receptor subtypes. For example, varenicline (Chantix) seems to be effective because it stimulates some subtypes strongly but others in only a limited way.

Kenny: Right. It's all about balance. The therapeutic window you want to reach is the one in which you can control the person's urge to smoke, but avoid the precipitation of withdrawal symptoms.

The dosage of a compound can affect which receptor populations it strikes, and we have shown that this is true of nicotine as well. Nicotine at low doses activates the high-affinity $\alpha4\beta2$ and other receptor subtypes that are responsible for many of its pleasurable and other effects. At higher doses, the drug begins to hit $\alpha5$-containing receptors in the habenula, which underlie aversive effects such as inhibition of reward systems.

Rose: That observation has tremendous treatment potential. It suggests that one could get a very strong combination effect with a dual-action compound that activated the $\alpha4\beta2$ receptors and also allosterically modulated the $\alpha5$-containing receptors. The first action would relieve withdrawal and supply some of nicotine's desirable effects, and the second action would trigger aversive effects if the individual smoked.

Kenny: Yes. While nicotine's effects on the nicotinic receptors and consequently on various neurotransmitter systems make sense as first places to look for an understanding of nicotine addiction, the drug also produces a large constellation of intracellular effects on signaling molecules and pathways. For example, nicotine can turn various kinases, phosphatases, and acetylases on or off. Hence, there are many other potential targets for therapeutic development within neurons. A further example of the potential of non-neurotransmitter, nonreceptor targets are the findings of George Uhl and other geneticists who are producing evidence that molecular processes classically thought to be involved in brain development are also implicated in addiction.

As the field progresses in coming years, we will likely be looking for answers in domains of neuroscience that currently are not typically considered relevant to addiction.

A wager

AS&CP: If you had $1,000 to bet on which strategy is going to bring the next large incremental advance in smoking control, what would it be?

Rose: I would put my money on the user-friendly form of inhaled nicotine that we have been developing in my laboratory. We have shown that people can self-administer nicotine in a particle form that produces more satisfaction, less irritation, and more rapid rises in blood levels than they get from the currently available nicotine vapor system. I think the impact on smoking rates will be dramatic. People will still be self-administering nicotine, but most authorities believe that nicotine constitutes less than 10 percent of the danger of smoking. I want to disclose a financial interest, because Philip Morris International just bought the patent rights to the approach.

Bevins: I'm going to bet on policy changes. For example, how about providing everyone easy and inexpensive access to whatever antismoking intervention they want? The health care savings that we would gain by making the whole range of smoking cessation interventions highly affordable and available would easily pay back the taxpayers.

Kenny: I'm going to split my money into three $333 bets. First, I agree with Jed that nicotine and nicotine-like compounds have untapped promise. My own bias in this respect is for compounds that modulate the $\alpha5$-containing receptors.

Second, there are other regulatory pathways that might produce breakthroughs. The authors discuss the GABA and glutamate pathways, but there are others. For example, Bill Corrigall has shown that the hypocretin pathway has very profound effects on nicotine-seeking behavior in rodents.

Finally, there are entirely new directions that we might go in. Some medications that are already available for treating cancer, cardiovascular disease, or diabetes may be effective for smoking. Some of these influence systems that there is currently no reason to believe might play a role in smoking, yet they may be central to the process.

We may already have a great compound out there. We just don't know it yet.

Rose: That raises an excellent point. We could potentially learn a great deal from clinical trials that are conducted on a wide range of conditions if they were to collect information on smoking. It has been especially frustrating when clinical trials that test compounds for conditions that are highly associated with smoking, such as cocaine abuse, don't measure the impact on smoking. After all, bupropion was developed because of the observation that people treated for depression reported changes in their smoking.